REMARKS/ARGUMENTS

Reconsideration and withdrawal of the rejections of the present application are respectfully requested in view of the amendments to the claims and remarks presented herewith, which place the application into condition for allowance.

Status of the Claims and Formal Matters

Claims 1, 12-15, 157 and 179 are currently pending in this application. By this paper, Claims 2 and 3 have been cancelled, and Claims 1 and 157 have been amended, without prejudice, and solely to expedite prosecution pursuant to the U.S. Patent and Trademark Office Business Goals (65 Fed. Reg. 54604 (September 8, 2000)). Applicants assert the right to reclaim cancelled subject matter in co-pending applications.

No new matter has been introduced by these amendments. Support for the amended recitations and new claim 179 can be found throughout the specification as originally filed, such as, for example, Original Claim 2 and at page 65, line 18.

Priority Claim

The Office Action contends that the disclosure of the prior-filed application U.S. Provisional Application No. 60/361,759 allegedly fails to provide adequate support or enablement in the manner provided by 35 U.S.C. §112, 1st paragraph, for one or more claims of the present application. According to the Office Action, the disclosure of U.S. Provisional Application No. 60,361,759 ("the '759 application"), filed on March 4, 2002, is drawn to the use of histone deacetylase inhibitors, including SAHA, for inducing terminal differentiation of neoplastic cells. The Office Action further contends that the '759 application provides a method of treating a patient "having a tumor," wherein the term "tumor" is defined as any cancer caused by the proliferation of neoplastic cells, "such as lung cancer, acute lymphoid myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, bladder melanoma, renal carcinoma, breast carcinoma, prostate carcinoma, ovarian carcinoma, or colorectal carcinoma" and alleges that the treatment of leukemia is not disclosed or supported by the '759 application. Thus, the Office

Action has afforded the instant application a priority date of October 24, 2003, the filing date of the instant application. Applicants respectfully disagree.

The amendments to the claims presented herewith recite a method for treating acute leukemia in a subject, comprising oral administration of a total daily dose of 400 mg of SAHA. "Acute leukemia" is expressly disclosed at, *inter alia*, page 11, line 13 of the '759 application. The '759 application, at page 16, 2nd paragraph, discloses that the compounds of the present invention can be administered as a single dose when administering up to 400 mg to the patient. In addition, on page 21 of the '759 application, Table 1 discloses administration to patients an oral SAHA dose of 400 mg QD on a continuous schedule.. "QD" is defined at line 11, page 21 of the '759 application as dosing once a day. Consequently, the instant claims are clearly supported by the disclosure of the '759 application, and should be afforded the priority date of **March 4, 2002**, not October 24, 2003.

Rejections under 35 U.S.C. §103(a)

Claims 1-3 and 157 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Vrana et al (Oncogene, 1999, vol. 18, pages 7016-7025; hereinafter "Vrana") and Amin et al (British Journal of Haematology, 2001, Vol. 115, pages 287-297; "Amin") in view of Curley et al (Proceedings of ASCO, 2002, vol. 21, page 6b, entry 1831; "Curley"). Claims 2 and 3 have been cancelled herewith, and as such, the rejection as applied to these claims should be withdrawn. Vrana allegedly teaches that SAHA induces apoptosis in U937 human leukemia cell cultures. Vrana, however, is silent regarding the treatment of leukemia orally in a subject *in vivo* using the instantly claimed dose of 400 mg.

The Examiner contends that Amin,discloses that histone deacetylase inhibitors such as SAHA induce caspase-dependent apoptosis in acute promyelocytic leukemia. Amin is critically deficient - Amin fails to teach or suggest the instant claimed dose of 400 mg.

The Examiner has used Curley to provide the missing dosage information. However, Curley is not prior art. The priority date of the instant application is March 4, 2002. The Curley abstract was presented at an annual meeting of the American Society of Clinical Oncology in

May 2002. Thus, the claim of priority of the instant application of March 4, 2002 pre-dates the publication of Curley. As discussed above, the remaining references Vrana and Amin, whether considered separately or together, do not fulfill the requirements of *prima facie* obviousness under §103(a) -- they are totally deficient. The combination of Vrana and Amin do not teach or suggest all of the instant claim limitations, namely methods of orally administering SAHA to treat acute leukemia in patients at a total daily dose of 400 mg. In view of the foregoing, the §103(a) rejections over Vrana, Amin, and Curley should be withdrawn.

Claims 12-15 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Vrana, Amin, and Curley and further in view of Grant et al (U.S. Application Publication No. 2005/0004007; "Grant") and Kabadi (EP 0 547 000; "Kabadi"). The Office Action alleges that Grant teaches oral administration of agents, including the instantly claimed SAHA, but fails to teach or suggest microcrystalline cellulose, croscarmellose sodium, and magnesium stearate as components of the pharmaceutical compositions disclosed therein. Kabadi allegedly teaches a pharmaceutical composition for oral administration comprising fluvastatin, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. Applicants traverse.

As discussed above, Curley cannot be used in support of an obviousness rejection under §103(a), because Curley published in May 2002 is not prior art -- it post-dates the priority date of the instant application of March 4, 2002. The combination of Vrana, Amin, Grant, and Kabadi, each considered alone or together, fail to teach or suggest all of the instant claim limitations, as required to establish *prima facie* obviousness under §103(a). In particular, Grant teaches combination therapy of an agent that induces cell differentiation (such as HDAC inhibitors) with a cyclin-dependent kinase inhibitor selected from flavopiridol, UCN-01, roscovitine, olomoucine, and butyrolactone. Grant does not teach monotherapy of SAHA. Because none of Vrana, Amin, Grant, or Kabadi teach or suggest methods of orally treating acute leukemia in a patient by administering a total daily dose of 400 mg of SAHA, Applicants request withdrawal of the §103(a) rejection.

Claims 1-3 and 157 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Vrana, Amin, and further in view of Breslow et al (U.S. Patent No. 6,087,367;

"Breslow"). Claims 2 and 3 have been cancelled herewith, and the rejection is moot as applied to these claims. The Office Action states that while Vrana and Amin do not teach treating "subjects" with leukemia by oral administration of SAHA, Breslow allegedly teaches methods of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells by administering oral or parenteral SAHA to a patient. Breslow does not cure the deficiencies of Vrana and/or Amin.

The combination of Vrana and Amin are deficient because they fail to teach or suggest all of the instant claim limitations, namely treatment of acute leukemia in patients by oral administration of a total daily dose of 400 mg of SAHA. Breslow fails to cure the deficiencies of Vrana and Amin, because Breslow is also silent regarding treating acute leukemia in patients by orally administering SAHA at a total daily dose of 400 mg. Breslow does not expressly disclose the instantly claimed oral doses and dosage regimens of SAHA

Because of the deficiencies described herein, namely the failure of Vrana, Amin, and Breslow to teach or suggest all of the instant claim limitations, Applicants respectfully contend that a *prima facie* case of obviousness under §103(a) has not been met. Consequently, reconsideration and withdrawal of the instant §103(a) rejection are respectfully requested.

Claims 12-15 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Vrana, Amin, and Breslow and further in view of Grant and Kabadi. Grant relates to combination therapies of an HDAC inhibitor and a cyclin-dependent kinase inhibitor, and does not disclose monotherapy of SAHA. Kabadi merely refers to excipients and does not cure the deficiencies of Vrana, Amin, Breslow, and Grant.

Neither Grant nor Kabadi cure the defects of Vrana, Amin, and Breslow. Grant relates to pharmaceutical compositions comprising a combination of an HDAC inhibitor and a cyclin B inhibitor, but do not teach monotherapy of HDAC inhibitors. Notably, Grant is silent regarding orally administering SAHA at a total daily dose of 400 mg to treat patients with acute leukemia. Kabadi relates to stabilized pharmaceutical compositions of HMG-CoA reductase inhibitors such

as fluvastatin, and like Grant, is also silent regarding oral administration of a total daily dose of 400 mg of SAHA to treat patients with acute leukemia.

For at least all of these reasons, Applicants respectfully request withdrawal of the §103(a) rejection over Vrana, Amin, Breslow, Grant, and Kabadi.

CONCLUSION

Favorable action on the merits is respectfully requested. If any discussion regarding this Amendment is desired, the Examiner is respectfully urged to contact the undersigned at the number given below, and is assured of full cooperation in progressing the application to allowance.

Applicants believe no additional fees are due with the filing of this Response. However, if any additional fees are required or if any funds are due, the USPTO is authorized to charge or credit Deposit Account Number: **50-0311**, Customer Number: **35437**, Reference Number: **24852-513**.

Respectfully submitted,

Dated: December 20, 2007

Michelle A Iwamoto

Ivor R. Elrifi, Reg. No. 39,529
Michelle A. Iwamoto, Reg. No. 55,296
Attorneys/Agents for Applicants
c/o MINTZ, LEVIN, *et al.*
666 Third Avenue-24th Floor
New York, New York 10017
Telephone: (212) 983-3000
Telefax: (212) 983-3115